DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 316

[Docket No. 85N-0483]

RIN 0905-AB55

Orphan Drug Regulations

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing regulations to implement section 2 of the Orphan Drug Act, which consists of four sections added to the Federal Food, Drug, and Cosmetic Act. The Orphan Drug Act directs the agency to provide written recommendations on studies required for approval of a marketing application for an orphan drug. It provides for the designation of drugs, including antibiotics and biological products, as orphan drugs when certain conditions are met, and it provides conditions under which a sponsor of an approved orphan drug enjoys exclusive approval for that drug for the orphan indication for 7 years following the date of the drug's approval for marketing. Finally, section 2 of the Orphan Drug Act encourages sponsors to make orphan drugs available for treatment on an "open protocol" basis before the drug has been approved for general marketing. These proposed regulations specify the procedures for sponsors of orphan drugs to use in availing themselves of the incentives provided for in the Orphan Drug Act and set forth the procedures FDA will use in administering it. These new provisions are intended to benefit consumers by encouraging manufacturers to develop and make available to patients drugs for diseases and conditions that are rare in the United States.

DATES: Comments by April 1, 1991.

ADDRESSES: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, room 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Emery J. Sturniolo, Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4718.

SUPPLEMENTARY INFORMATION:

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I. Background

In enacting the Orphan Drug Act (Pub. L. 97-414), Congress sought to promote the development of drugs, including antibiotics and biological products, that are needed by, but not available to, people in the United States with "rare diseases or conditions." Congress recognized that the market for drugs intended to treat people with rare diseases or conditions is so limited that the cost of developing the drugs makes a profit by the developer unlikely. Congress concluded that changes in Federal laws were necessary to create incentives for the development of these drugs. Accordingly, Congress enacted the Orphan Drug Act, which included amendments to the Federal Food, Drug, and Cosmetic Act (the act), to create incentives for the development of these drugs by providing, among other incentives, protocol assistance to sponsors of drugs for rare diseases and a 7-year period of exclusive marketing to the holder of the first approval of a designated orphan drug for the orphan indication (21 U.S.C. 360aa-dd).

These proposed regulations, which codify existing administrative practices that implemented the Orphan Drug Act of 1983 and its subsequent amendments (see section II.B. of this preamble), would establish procedures to provide for protocol assistance and to govern exclusive marketing approval. The Orphan Drug Act provides these incentives to assure that drugs that would not otherwise be developed are in fact developed. Thus, these proposed regulations will, where possible, attempt to ensure that the act's incentives are granted only when they would further the purposes of the Orphan Drug Act.

The main purpose of the Orphan Drug Act is to stimulate innovation in developing treatments for patients with rare diseases and conditions and to foster the prompt availability of therapeutically superior drugs. These proposed regulations attempt to ensure that improved therapies will always be marketable, and that orphan drug exclusive approval does not preclude significant improvements in treating rare diseases.

II. Contents of the Program

A. Recommendations for Investigations of Drugs for Rare Diseases or Conditions

Proposed § 316.10 sets forth the procedure for a sponsor to take advantage of section 525 of the act (21 U.S.C. 360aa), which encourages a sponsor of a putative orphan drug to request FDA to provide written recommendations for the nonclinical and clinical investigations required to achieve marketing approval.

Section 525 of the act was intended to reduce the wasted expense and lost time that occur when sponsors carry out investigations under protocols that are unsatisfactory to FDA. This section states that a sponsor may be provided such written recommendations "* * * [if there is] reason to believe that a drug for which a request is made under this section is a drug for a disease or condition which is rare in the States." The provision does not require that a sponsor have actually obtained orphan-drug designation for the subject drug at the time of the request.

FDA has, therefore, determined that, although a review of the sponsor's submission as to whether there is "reason to believe" that the subject drug is an orphan drug would be required for requests for written recommendations, the information and documentation of orphan-drug status to be filed by sponsors with such requests can be less extensive than that required under proposed § 316.20 for designation of an orphan drug under section 526 of the act.

FDA understands that the Orphan Drug Act was enacted to provide incentives, including early agency advice, to sponsors of orphan drugs. The agency believes, however, that it remains the sponsor's responsibility to design and carry out the development of a drug. FDA is neither in a position to design the needed studies *de novo* nor to review the relevant literature or other information on the drug and the disease to be treated to facilitate planning of the development program. So that FDA can provide informed comments on the adequacy of any proposed nonclincial or clinical protocols, the sponsor must include a detailed outline of the proposed study as specified in proposed § 316.10(b) in any request for written recommendations.

FDA intends that any recommendation provided under section 525 of the act and proposed § 316.12 would be the equivalent of an advisory

opinion under § 10.85 (21 CFR 10.85) of FDA's administrative practices and procedures regulations. The agency would make every effort to adhere to the advice given with respect to the design of studies and the kinds and amounts of data needed for a sponsor's orphan drug to be approved (or licensed) for marketing. FDA may later modify a recommendation if new information becomes available that would place reliance on the recommendation in conflict with good science or the public health. With this exception, however, if a sponsor responsibly follows recommendations related to studies critical to approval, and if the results of the ensuing studies support the safety and effectiveness of the drug, such studies should result in the generation of adequate data to support a marketing application.

Proposed § 316.14 sets forth the reasons why FDA may refuse to provide written recommendations for the nonclinical or clinical investigations required for marketing approval of an orphan drug. The agency expects that most of these reasons will serve as a basis for an agency inquiry to the sponsor seeking more information rather than for an outright refusal to provide such recommendations. However, the sponsor's failure to supply information respecting the results of nonclinical laboratory studies or completed early clinical studies as required by proposed § 316.12(d) or to reply to correspondence respecting the sponsor's request within 90 days as required by proposed § 316.14(c) would lead to a refusal to provide recommendations.

B. Designation of Orphan Drugs

Orphan-drug designation must be obtained before a sponsor can obtain any direct financial benefits that are provided by the Orphan Drug Act. Eligibility for tax credits, for orphan-drug exclusive approval, and for grants and contracts depends upon the sponsor's drug having been designated under section 526 of the act (21 U.S.C. 360bb) as a drug for a specified disease or condition which is rare in the United States. FDA's experience with orphan—drug designations reveals that sponsors have requested designation at all stages in a drug's development, even after FDA's approval of a drug's marketing application. For an interim period after enactment of the Orphan Drug Act on January 4, 1983, FDA provided a grace period during which the agency accepted requests for designation of certain drugs and designated them as orphan drugs after FDA had approved the marketing applications for them. For reasons discussed in a notice published in the **Federal Register** of February 5, 1986 (51 FR 4505), this interim policy was terminated on May 6, 1986. In addition, in Pub. L. 100–290 (the Orphan Drug Amendments of 1988), Congress amended section 526 of the act to require that requests for designation must be made before the submission of a marketing application (see 53 FR 47577; November 23, 1988).

To be designated an orphan drug, a sponsor must show: (1) That the drug is being or will be investigated for a specified rare disease or condition; (2) that the drug would be subject to approval under section 505(b) or 507 of the act (21 U.S.C. 355(b) or 357) or to licensure under section 351 of the Public Health Service Act (42 U.S.C. 262); and (3) that the marketing approval would be for such use or condition.

The 1984 amendments to the Orphan Drug Act (The Health Promotion and Disease Prevention Amendments of 1984) (Pub. L. 98–551) introduced a prevalence figure of 200,000 affected persons as a ceiling for a "rare disease or condition." If a disease or condition affects more than this number, a showing (pursuant to proposed § 316.21) that there is no reasonable expectation that the cost of developing and making available the drug to treat the disease or condition will be recovered from sales in the United States must be made before a drug can be considered an orphan drug.

Congress provided that the 200,000 prevalence figure means 200,000 affected persons in the United States at the time that the orphan-drug designation request is made (not 200,000 new cases annually). Under this proposal, if a drug is designated as an orphan drug because it is intended for a disease or condition with a prevalence of under 200,000, the drug would remain an orphan drug even if the disease or condition ceases to be an orphan disease or condition because of increased prevalence. This approach would protect a sponsor's good-faith investment.

Proposed § 316.29 does provide for discretionary suspension or revocation of orphan-drug designation and, thus, exclusive marketing rights if it is later found that the application for orphan-drug designation: (a) Contained an untrue statement of material fact; or (b) omitted material required information. Also, FDA may suspend orphan-drug designation if it subsequently finds that, as of the date of the submission of the designation request, the drug had in fact not been eligible for designation.

An indication for treatment of a specific disease or condition could involve all patients with that disease or condition or a specified subpopulation of those with the disease or condition. If a drug is under development for only a subset of those persons with a particular disease or condition, orphan-drug designation for use in the limited subset may be granted. Exclusive approval for a disease subset would not bar approval of the same drug for the larger population or other subsets of population by different sponsors, however, if that were later deemed appropriate. In diseases or conditions which are common, subsets would qualify for designation only if the subset is medically plausible. For example, a drug might well be too toxic for use in treating a disease or condition except in patients refractory to or intolerant of other less toxic treatments; the refractory and intolernat patients might be a reaonable orphan subset. On the other hand, choosing an arbitrary subset (e.g., people with blood pressure over a certain level), simply to qualify a drug as an orphan-drug would be unacceptable.

FDA notes that proposed indications for use of orphan drugs are subject to review by the applicable FDA center (e.g., the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research). The centers routinely review indications for use during the approval process. Also, FDA's Office of Orphan Products Development may ask the centers for their advice about the medical plausibility of potential orphan-drug designations. These reviews by the centers include consideration of the appropriateness of the request for orphan-drug designation, and, in particular, consideration of whether the target populations have been artificially restricted.

For most orphan drugs, only one sponsor has requested orphan-drug designation, although in some instances two or more persons each has sought orphan-drug designation for the same drug for the same indication. FDA intends to ensure, however, that a pioneer sponsor's research is not used to give a second sponsor a "free ride." Accordingly, in § 316.20(a), FDA proposes to require that each sponsor's designation request contain all the information needed to allow a determination as to the appropriateness of designation of the product as an orphan-drug even when another sponsor has obtained such designation for the same drug for the same indication is no bar to designation (or, indeed, exclusive approval) of the same drug for a new orphan indication, and § 316.20(a) so provides.

FDA recognizes that a finding of eligibility for orphan-drug status under the prevalence criteria could apply to all sponsors of drugs for the disease or condition in question. However, FDA believes it unfair to allow a subsequent sponsor to use a pioneer sponsor's research data for the purpose of obtaining orphan-drug designation when such research data would by law not otherwise be available to the subsequent sponsor.

In all cases, the indication for which a drug is designated would have to be the same as, or equivalent to, the ultimately approved indication for exclusive approval to take effect.

FDA understands that the target population for use of a vaccine, diagnostic drug, or preventive drug may be an "at-risk" population that is larger than the population actually affected by the disease or condition. For this reason, proposed §§ 316.20(b)(8) and 316.21(b)(3) would require that sponsors include in any request for designation of such a drug an estimate of the number of people to whom the vaccine, diagnostic drug, or preventive drug will be administered annually in the United States. FDA believes that this provision is justified for such drugs because, even though certain vaccines (e.g., polio vaccine) and other diagnostic/preventive drugs are for rare disorders, they clearly are not orphan drugs because they may be administered to the at-risk target populations of millions of people and thus are not within the class of products contemplated to be covered by orphan-drug legislation.

Under proposed § 316.22, the agency would require foreign sponsors that seek orphan-drug designation to name a permanent-resident agent to whom communications may be made.

Under proposed § 316.26(a), FDA enumerates the reasons for which it would refuse to grant a sponsor's request for orphan-drug designation. In many respects, the reasons why FDA would under § 316.26 deny orphan-drug designation parallel the reasons why FDA may under § 316.14 refuse to provide written recommendations on investigations. As an exception to the general rule, however, proposed § 316.26(b) also provides that FDA may refuse to grant a request for orphan-drug designation if the request contains an untrue statement of material fact. FDA believes that refusal to grant a request in such a circumstance should be discretionary and not mandatory; for example, the untrue statement may be inadvertent.

On the whole, FDA would liberally grant orphan-drug designation when the threshold prevalence or profitability tests are met. FDA would grant orphan-drug designation even for a drug that is otherwise the same drug as one already given exclusive marketing approval under proposal subpart D of part 316 (and during the first drug's period of exclusive approval) when the second sponsor can make a plausible showing that it may be able to produce a clinically superior drug. Approval of such a subsequent drug during the first drug's period of exclusive approval for treatment of the same rare disease or condition would require evidence of the clinical superiority of the subsequent drug, however. The content of this evidence will depend on the nature of the superiority claimed. (See the discussion of the definition of "clinically superior" below.)

FDA considered proposing a rule under which it would designate drugs apparently the same as drugs that already have orphan-drug exclusive approval only where the agency believed that there was a high probability of eventual approval. Such a rule would exclude most drugs that are identical as to active moiety to already approved orphan drugs. FDA decided on a liberal designation policy, however, because the agency wants to encourage research whose aim is to produce safer and more effective drugs, even if FDA believes that the prospects are dim (because of the anticipated difficulty of demonstrating clinical superiority) for eventual marketing approval. FDA believes that a liberal designation policy is appropriate despite the possibility that it might lead to wider use of the tax credit provisions under section 4 of the Orphan Drug Act because the agency doubts that sponsors will deliberately conduct fruitless research just to obtain the tax credits.

Also, the agency is proposing to allow sponsors to apply for amendments to orphan-drug designation up to the time of approval of their marketing applications. The purpose of this proposal is to allow for situations in which testing data unexpectedly demonstrate the effectiveness of drugs in different populations or for different diseases or conditions from that which the drug was initially designated. FDA would grant such an amendment request only if it found that the initial designation request was made in good faith and that the amendment is sought only to render the orphan-drug designation consistent with unanticipated test results. If the prevalence of the disease or condition named in the amendment request exceeds 200,000 people in the United States as of the date of submission of the amendment request, of course, the amendment could not be granted and the drug, when ultimately approved for the new or expanded indication, might be ineligible for exclusive marketing status under the Orphan Drug Act.

FDA is aware that, under Public Law 100–290, no orphan-drug designation request can be granted after the submission of a marketing application. However, FDA does not believe that Congress thereby intended to preclude an amendment to an already existing application for purposes of conforming the designation to the test results.

FDA proposes that this regulation, when final, will apply only prospectively. Therefore, FDA does not plan to reconsider any prior actions under the Orphan Drug Act, or change any orphan-drug status, to conform to the final regulation.

C. Verification of Orphan-Drug Status

An important feature of the definition of an orphan drug is the prevalence figure of 200,000 affected people in the United States as a ceiling for a "rare disease or condition." In accordance with this principle, which was introduced into the Orphan Drug Act by Public Law 98–551 (see section II. B. of this preamble), proposed § 316.21 requires that sponsors of would-be orphan drugs that are designed to treat a condition or disease that affects 200,000 or more persons file detailed statements, including information about marketing costs and justification for revenue projections for the drug. Further, at FDA's request, a sponsor would be required to open its books, including financial records and sales data with respect to the drug proposed for orphan-drug designation, to FDA-appointed auditors. Failure to do so or failure adequately to justify its claims would result in denial of a sponsor's designation request.

FDA recognizes that these data and analysis requirements may be burdensome. FDA believes, however, that the data and information required by proposed § 316.21 to be made available to the agency are necessary to a demonstration of lack of profitability. Allocation of costs is sometimes debatable, and a full disclosure of all cost and profit information related to the drug in question both in the United States and abroad is necessary to satisfy the agency that the sponsor has fulfilled its burden of demonstrating a lack of profitability. However, FDA solicits comments on ways to minimize costs to sponsors while allowing the agency to ascertain a lack of profitability when that is claimed by the sponsor.

The requirement that sponsors open their books at reasonable times on demand for examination by FDA-appointed auditors is necessary to enable FDA to verify claims made in orphan-drug designation requests. However, FDA does not expect to exercise the authority to examine companies' books often.

D. Orphan-Drug Exclusive Approval

Section 527 of the act automatically vests a 7-year period of orphan-drug exclusive approval on the date that the agency issues a marketing approval for a designated orphan drug. For this reason, no further action by FDA to bring about exclusive approval is necessary. Under proposed § 316.34, however, the agency would send the sponsor of an approved, designated, orphan drug timely written notice recognizing exclusive approval.

FDA interprets the act to accord exclusive approval only to the first drug approved. This interpretation means that other applicants, who may have invested substantial money and effort in supporting their applications, are barred from marketing for the 7-year period of exclusivity even though they filed before or shortly after the applicant whose product was approved. Because of this, some have argued for "joint exclusivity" between or among "temporally close" competitors, that is, sponsors that submit marketing applications prior to the first approval of the drug.

FDA is required by law to reject the concept of joint or shared exclusivity (unless it is agreed to by all sponsors of a particular drug). The act provides that, after approval of an orphan drug, "* * * [FDA] may not approve another application * * * for such drug for such disease or condition for a person who is not the holder of such approved application * * * until the expiration of seven years from the date of approval of the approved application * * *" (21 U.S.C. 360cc(a)). The agency interprets this language to preclude the possibility of shared or joint exclusivity except where agreed to by the sponsor of the drug with the right to exclusive marketing.

E. Scope of Exclusive Approval

Exclusive marketing is the Orphan Drug Act's primary incentive for the development of orphan drugs. Thus, FDA has intensively considered how it would determine whether one drug is the same as another with respect to orphan-drug exclusive marketing. Historically, any difference in the chemical structure of a drug's active moiety (that part of the molecule other than the parts that make it a salt or ester), whether or not that difference caused a difference in the clinical effect, rendered the drug containing that active moiety a new molecular entity. This distinction antedated any considerations of exclusivity and was principally a classification matter. It reflected the view that the modified drug had a high probability of being different from the original in its actions or toxicity and would need to undergo full toxicologic and clinical testing because it was not possible to tell from examining the structure of the two molecules or performing simple in vitro or in vivo tests whether they would behave identically, FDA was, thus, not prepared to allow "shortcuts" to marketing approval for modified active moieties under any circumstances, no matter what the agency's view of the likely significance of the structural changes and no matter how small they were.

At the same time, it is often possible to modify a small molecule while retaining its desired effect. The ability to do this has been used by sponsors to develop their own versions of popular widely used drugs to avoid infringements of existing patents. Thus, sponsors have in recent years developed modified angiotensin converting enzyme inhibitors, calcium channel blockers, H2-antihistamines, beta-adrenergic blocking agents, steroids, and cephalosporin antimicrobials. While a major aim of the sponsors may have been development of a distinct molecule that would not be restricted by existing patents, sponsors have also been interested in distinguishing their drug therapeutically from a competitor's. The modified molecules were often pharmacologically distinct, sometimes in ways that were quite advantageous, such as by having greater specificity, by lacking a particular adverse effect, or by having different pharmacokinetics.

With respect to small molecules, it appears sound, for the purposes of consideration of exclusive marketing under the Orphan Drug Act, to adopt a policy that regards two drugs as different if they differ with respect to the chemical structure of their active moieties. First, such differences are highly likely to lead to pharmacologic differences. Second, the development of an agent with a novel active moiety is not a financially or intellectually trivial matter; it represents a considerable effort and a substantial risk, as the results of changes in small molecules are difficult to predict.

It would be possible to have the same policy for macromolecules, i.e., to regard any difference in structure, or even any uncertainty about actual structure (e.g., a preparation may contain an array or distribution of closely related molecules or be of such a complex nature that it cannot be precisely defined), as causing two drugs to be considered different. However, the differences in structure/function relationships between macromolecules and small molecules could suggest the need to articulate a different policy for macromolecules.

Some degree of heterogeneity is common in the case of macromolecules; if this were to lead to the conclusion that two products composed of macromolecules were almost always different, there would be little or no exclusive marketing associated with macromolecules, probably not the outcome sought by Congress in enacting the Orphan Drug Act. Also, unlike with small molecules, it is possible to make changes in macromolecules that are very likely to have no pharmacologic effect (e.g., a substitution of one amino acid for another similar one at an unimportant site in the molecule), but that could nonetheless defeat exclusive marketing if any structural difference were sufficient to make drugs different for purposes of orphan-drug exclusive marketing. Again, this is an outcome that might not be consistent with the intent of the Orphan Drug Act.

Because small differences may affect the function of macromolecules much less than that of small molecules, it may be appropriate that certain chemical differences or uncertainties about chemical structure of macromolecules should not cause two drugs to be considered different for purposes of the Orphan Drug Act, unless the chemical differences were associated with improvements in clinical effect. If this policy were implemented, it would be critical to define the kinds of differences in clinical effect that would be considered sufficient to support a conclusion that the drugs were different.

It would be easiest to show that a new drug was different from the innovator drug if any documented pharmacologic difference between the drug were considered a sufficient basis for determining that the drugs were different. Conversely, it would be relatively difficult for a new drug to be considered different if a clear clinical advantage had to be demonstrated.

One can describe several alternative scientifically reasonable sets of criteria for identifying drugs as different for purposes of determining orphan-drug exclusive marketing rights. The crucial differences among them are in how much structural distinction there must be between a drug and a potential competitor and whether the structural

distinction must be linked to functional differences for the competitor drug to be considered a "different" drug on chemical/structural grounds for purposes of the Orphan Drug Act. In each case, even a drug considered the "same" drug structurally could become a "different" drug for these purposes by showing clinical superiority. Four possible criteria for determining sameness/difference are discussed below:

1. Two drugs would be considered different if they had any defined structural difference (other than being different salts or esters of the same active moiety), such as a different amino acid sequence or glycosylation pattern, or if they had heterogenous structures (e.g., a polysaccharide with an array of molecules having different numbers of the same repeating saccharide unit and thus different chain lengths) or, for other reasons, had a structure that could not be precisely defined.

Comment: This criterion applies similar considerations to small and large molecules. Macromolecular drugs with similar structures and similar, even identical, pharmacologic activity would usually be treated as different drugs. Because it is often not possible completely to define all aspects of the structure of macromolecules, few closely related macromolecules would be considered the same drug, although there would be some cases, for example, two human growth hormones with identical amino acid sequence and no glycosylation, in which identity would be presumed. Using this criterion, orphan-drug exclusive marketing would rarely prevent the development of a competitor macromolecular drug so long as the competitor were willing to support development of a full new drug application (NDA) or product license application (PLA).

2. Two drugs would be considered different if they could be shown to have a defined structural difference, as above. However, they would not be considered different simply because of uncertainty about their precise structure or because the drugs are somewhat indeterminate mixtures. For example, two polypeptide or protein molecules that had the same primary, secondary, and tertiary structures, insofar as could be determined, or had uncertain or mixed chemical structures that could not be distinguished, would be considered the same drug, unless the subsequent drug could be shown to be clinically superior.

Comment: This definition would be very similar to criterion 1 in practice, although it would be slightly more likely that competing products would be considered the same drug. The definition itself would create a strong incentive for sponsors to identify and define structural differences in previously indeterminate macromolecules, either through additional testing or minor manipulations in structure.

3. Two drugs would be considered the same drug if the principal, but not necessarily all, structural features of the two drugs were the same, unless the subsequent drug were shown to be clinically superior. This criterion would apply as follows to different kinds of macromolecules:

a. Two protein drugs would be considered the same if the only differences in structure between them were due to: (1) Post-translational events; or (2) infidelity of transcription or translation; or (3) minor differences in amino acid sequence. Other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the subsequent drug were shown to be clinically superior.

b. Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were post-polymerization modifications, unless the subsequent drug could be shown to be clinically superior.

c. Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, oxyribose, or modifications of these sugars) unless the subsequent drug were shown to be clinically superior.

d. Closely related complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, or some other traditional biological, would be considered the same unless the subsequent drug were shown to be clinically superior or to depend on different mechanisms of action.

Comment: This criterion makes a presumption of sameness, even in the case of proteins, in the face of minor differences in structure other than differences in the primary amino acid sequence if those differences occur after the basic amino acid change is translated from the RNA. Sameness is also presumed even in the face of amino acid sequence differences if they are "minor".

Determining whether differences in amino acid sequences should be considered minor involves judgment and could lead to legal challenges of FDA decisions. An alternative approach would be to allow any difference in amino acid sequence to cause a molecule to be considered different. With that approach, however, a second sponsor could then introduce an inconsequential difference in amino acid sequence solely to defeat orphan-drug exclusion marketing. Overall, the approach embodied in criterion 3 would, compared to the first two approaches, tend to increase the likelihood that a potential competitor would be barred by the Orphan Drug Act from marketing a variant of an already marketed orphan drug.

4. Two similar macromolecules would be considered the same unless their structures differed in ways that could reasonably be expected to influence relevant pharmacologic activity. Other structural differences would not cause the second drug to be considered a different drug unless the subsequent drug were shown to be clinically superior.

Comment: Like criterion 3, this approach makes a relatively strong presumption of sameness for pharmacologically related drugs and would support orphan-drug exclusive marketing of the first approved drug in the face of considerable differences in structure. This approach depends even more than does criterion 3 on judgment in that the kinds of structural differences likely to be related to differences in pharmacological activity are not specified. However, in this case, the agency would have to determine that a particular structural change was likely to be associated with a clinical difference without necessarily requiring evidence from clinical studies that it actually did lead to such a difference. This would entail making a complex and potentially controversial judgment.

All of the above four criteria are scientifically reasonable, and selection of one involves policy considerations as much as scientific ones. Criteria 1 and 2 use the same criteria for determining differences between macromolecules that are used to determine whether small, well-defined drugs have the same active moieties. Criteria 3 and 4 are based on the premise that function of macromolecules is less directly related to minor structural differences than is the case for small molecules and incorporates an assessment of functional relevance into the comparisons.

The first two criteria give relatively little value to orphan-drug exclusive marketing for macromolecules, allowing any evidence of structural difference, or

uncertainty about structure, to cause two drugs to be considered different drugs. They are fairly easy to interpret. The subsequent drug sponsor would not get a free ride, as it would still have to carry out the studies necessary to support its own marketing application, a significant effort. However, that subsequent sponsor could proceed with a reasonably sure expectation of ultimately being able to market the drug.

The third criterion, which FDA is proposing to adopt, gives considerable protection to the first approved orphan product against a second sponsor's attempts to defeat exclusive marketing rights by introducing minor molecular changes. It would also be reasonably straightforward to implement; minor chemical differences simply would not cause a subsequent drug to be considered different unless the subsequent drug were shown to be clinically superior. FDA is proposing this option because it would seem to constitute the best available mechanism to protect the integrity of the chief incentive for orphan drug development that Congress created while allowing clinically superior drugs with similar chemical structure to be marketed. Criterion 4 leaves so much to discretion that day-to-day implementation could become a major problem. Choice of criterion 3 is consistent with discussions at the Institute of Medicine meeting held on November 19 and 20, 1990.

Under the test set forth under criterion 3, a drug would be considered different if it were shown to be clinically superior to an already approved orphan drug. FDA proposes that a drug be considered "clinically superior" to an already approved orphan drug when it provides a therapeutic advantage for at least one of the following three reasons:

(1) It has greater effectiveness than the approved orphan drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs. In most cases, direct comparative clinical trials would be necessary; or

(2) It has been shown to be safer in a substantial portion of the target population, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. Superior safety might also be proven where two drugs have approximately the same therapeutic effect but where the subsequent drug is shown to produce that effect at a lower dose and only where the first drug had significant side effects. In some cases, direct comparative clinical trials would be necessary; or

(3) In unusual cases, where the subsequent drug has not been shown to be safer or more effective, a subsequent drug could nevertheless qualify as being "clinically" or "therapeutically" superior through a demonstration that the product otherwise makes a major contribution to patient care.

This third basis for finding a subsequent drug to be clinically superior is intended to constitute a narrow category, and its proposed use is not intended to open the flood gates to FDA approval for every drug for which a minor convenience over and above that attributed to an already approved orphan drug can be demonstrated. The only situation that FDA has identified as potentially providing a "major contribution to patient care" without a clear showing of a gain in safety and/or effectiveness is the development of an oral dosage form where the first drug was available only in a parenteral dosage form. FDA solicits comments as to whether other kinds of differences, such as differences in method or vehicle of administration, might constitute "major contributions to patient care." Because FDA has not been charged with making decisions on the approval of drugs based on cost, the agency proposes to rule out cost considerations in determining whether a drug makes "a major contribution to patient care."

It has been suggested that, whenever FDA is asked to approve a subsequent drug because it is "clinically superior" to the first-approved drug, the agency should give the sponsor of the first drug an opportunity to conduct studies showing that its drug matches the superior qualities of the subsequent drug. FDA proposes to reject this suggestion on grounds that it is not fair to the sponsor of this similar but nevertheless innovative drug to refuse to allow this subsequent sponsor the fruits of its testing and research. Also, giving the first sponsor this opportunity might delay the approval of a clinically superior drug, especially where the first sponsor is significantly behind in testing the clinically superior drug.

In any situation where FDA confronts a question of whether or not a subsequent orphan drug is the same as or different from an already approved first orphan drug, FDA proposes to place the burden of proof (including the burden of production of evidence and the burden of persuasion of FDA) on the sponsor of the subsequent drug who is contending that its drug is different. It is usual for FDA to require a sponsor to prove all aspects of its entitlement to market a product. Applied here, such a rule would better protect the integrity of the chief incentive that Congress created for orphan-drug development than would the placing of the burden on the exclusive marketing holder.

F. Inadequate Supplies

Under section 527 of the act, whenever the agency (and by delegation under 21 CFR 5.58(b), the Director, Office of Orphan Products Development (OOPD)) has reason to believe that the holder of an approved marketing application cannot assure the availability of sufficient quantities of an orphan drug to meet the needs of people with the disease or condition for which it was designated an orphan drug, the act provides that the agency may approve another application for the same drug for the same indication.

Proposed § 316.36 provides a procedure whereby the Director, OOPD, would notify the holder of the possible insufficiency and would request, within a specified time, that the holder (1) provide in writing or orally or both, at the Director's discretion, views and data as to how the holder can assure the availability of sufficient quantitites of the drug; or (2) consent to the approval of other marketing applications.

Following his or her decision in the matter, the Director would issue an order with findings and conclusions, either reaffirming or withdrawing the drug product's exclusive approval. Any such order which the Director issues would constitute final agency action. In the event the Director's decision is to withdraw the drug product's exclusive approval, FDA may approve any number of marketing applications even if the additional applicants cannot themselves assure the availability of sufficient quantities of the orphan drug in question. Congress' clear intent was to foster the development and marketing of sufficient supplies of drugs for rare diseases (H. Rept. 97–840, 97th Cong. 2d., p. 7, 1982). Marketing approvals of other sponsors' drugs would encourage orphan drug development even if the new marketing approval holder could not itself immediately guarantee adequate supplies either by itself or with other manufacturers.

Once exclusive marketing is broken under section 527 of the act for failure to assure the availability of adequate supplies, it cannot be restored even if the first manufacturer is later able to assure the availability of adequate supplies. It would be unreasonable to expect a second manufacturer to make a large investment in drug development to fill a gap if it could be shut out of the

market at any time that the original manufacturer could assure adequate supplies.

G. Open Protocols

In subpart E of proposed part 316, FDA commits itself to encourage sponsors of designated orphan drugs to design and implement treatment protocols to permit treatment of any patient with the rare disease or condition during investigations of the drug upon request by the patient's physician. FDA notes that, in FDA's experience to date, the vast majority of orphan drugs under investigation are being tested for "serious" or "immediately life-threatening" diseases as they are defined in 21 CFR part 312, and proposed § 316.40 so provides.

H. Availability of Information

FDA recognizes that designation requests will contain confidential commercial information and, indeed, that the very existence of an orphan-drug designation request may itself be confidential commercial information. In addition, a request for orphan-drug designation is in most instances supported by information that will be incorporated in a sponsor's marketing application. Release of such information prior to marketing approval of the sponsor's drug product could have an adverse impact on the sponsor's obtaining first approval and, thus, exclusive approval pursuant to section 527 of the act.

For all these reasons, proposed § 316.52(a) provides that no information submitted by a sponsor as part of a request for orphan-drug designation would be released by FDA to the public prior to such time as FDA takes final action on the request. This means that unless previously disclosed or acknowledged, FDA would not make public the existence of any pending orphan-drug designation request. Under proposed § 316.52(c), however, upon granting orphan-drug designation, FDA would publish the following information: the trade and generic names of the designated product, the uses for which the drug is designated, the date of the granting of orphan-drug designation, and the name and address of the sponsor of the drug receiving designation.

Proposed § 316.52(b) provides that, irrespective of whether the existence of a pending request for designation has been publicly disclosed or acknowledged, no data or information in the request are available for public disclosure prior to final FDA action on the request. Upon final FDA action on a request for designation, proposed § 316.52(c) provides that FDA will determine the public availability of data and information in the request in accordance with 21 CFR parts 20 and 21 CFR 314.430.

In accordance with proposed § 316.52(e), FDA will follow existing statutes and regulations in deciding whether to disclose publicly the existence of a pending marketing application for a designated orphan drug for the use for which the drug was designated. In general, FDA does not disclose the existence of the application unless it has been previously publicly disclosed or acknowledged or disclosure is otherwise required. Finally, proposed § 316.52(f) provides that FDA will determine the public availability of data and information contained in pending and approved marketing applications for a designated orphan drug for the use for which the drug was designated in accordance with part 20, § 314.430, and other applicable requirements.

I. Administrative Challenge Procedures

FDA does not propose to provide for a hearing on issues of the scope of exclusive approval or any other issues of approvability or orphan-drug designation under the Orphan Drug Act. Neither the Constitution, nor the Administrative Procedure Act, nor the Orphan Drug Act requires a hearing on any issue of this kind. Hearings are time-consuming and resource-intensive. FDA is not persuaded that a regulatory hearing before the agency under part 16 of FDA's administrative practices and procedures regulations (21 CFR part 16) is more likely to lead the agency to a correct result than is careful administrative review. Further, the agency notes that, if a challenging sponsor has sufficient information, it can, under current regulations, mount an effective challenge to an incipient drug approval by filing a citizen petition pursuant to 21 CFR 10.30.

FDA considered creating an administrative procedure, without a hearing, whereby the agency would give notice to the sponsor of an approved exclusively marketed orphan drug of the proposed approval of another sponsor's application for marketing a drug that, in FDA's view, is similar but not identical. Further, FDA considered the possibility of allowing the sponsor of the exclusively marketed drug an opportunity to challenge administratively the proposed approval of a subsequent drug.

FDA has decided not to propose a new administrative procedure for allowing challenges to incipient marketing application approvals or denials under section 527 of the act. Just as there is no requirement for a hearing, there is no requirement in the Constitution, the Administrative Procedure Act, or the Orphan Drug Act for such an administrative procedure. Also, postdecisional judicial review is preferable to an administrative challenge procedure because a predecisional challenge procedure would be time consuming and could be used for the sole purpose of delaying approval of competing drugs. Also, it would be difficult to determine who should have the right to challenge an incipient approval and who should be entitled to what notice of what anticipated agency action. Finally, a predecisional administrative challenge procedure would present difficulties due to the nondisclosability of relevant information under FDA's public information regulations (21 CFR part 20 and other regulations cited in that part).

For these reasons, FDA believes that the disadvantages of an administrative challenge procedure are too great to justify creating one.

J. Economic Impact

The agency has examined the economic impact of this proposed rule in accordance with Executive Order 12291 and the Regulatory Flexibility Act (Pub. L. 96–354) and concludes that this proposed rulemaking is not a major rule as defined by Executive Order 12291 and will not have a significant impact on a substantial number of small entities.

The proposed rule would codify existing administrative practices that implemented the Orphan Drug Act of 1983 and its amendments. Because the proposed rule introduces no new requirements, it imposes no incremental costs on industry or consumers.

It is clear that the Orphan Drug Act, as implemented by existing administrative practices, has significantly increased the rate at which new orphan drugs are marketed. While two or three drugs that might be eligible as orphan drugs were approved annually prior to the Orphan Drug Act, an average of eight designated orphan drugs have been approved per year and marketed since 1984. Moreover, orphan-drug designation has been granted to an average of 41 drugs per year since 1984. Thus, the Orphan Drug Act, as implemented since 1983, has provided an effective stimulus for the development and marketing of drugs for diseases or conditions that are rare in the United States.

K. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this proposed action is of a type that does not individually or

cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

L. Paperwork Reduction Act of 1980

This proposed rule contains information collections which are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1980. The title, description, and respondent description of the information collection are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information.

Title: Orphan Drug Regulations—NPRM.

Description: These proposed regulations specify the procedures for sponsors of orphan drugs to use in availing themselves of the incentives provided for in the Orphan Drug Act and set forth the procedures FDA would use in administering it.

Description of Respondents: Businesses or other for-profit organizations.

ESTIMATED ANNUAL REPORTING AND RECORDKEEPING BURDEN

Section	Annual number of respondents	Annual frequency	Average burden per response	Annual burden hours
316.10	6	1	125	750
316.20 and 316.21	28	1.78	125	6,250
316.22	3	1	2	6
316.27	5	1	4	20
316.36	1	3	15	45
Total				7,071

The agency has submitted a copy of this proposed rule to OMB for its review of these information collections. Comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, may be submitted to FDA's Dockets Management Branch (address above) and to the Office of Information and Regulatory Affairs, OMB, Washington, DC 20503.

M. Effective Date

FDA proposes that any final rule based on this proposal would become effective 30 days after the date of publication of the final rule.

N. Request for Comments

Interested persons may, on or before April 1, 1991, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 316

Orphan drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that 21 CFR part 316 be added as follows:

PART 316—ORPHAN DRUGS

Subpart A—General Provisions

Subpart B—Written Recommendations for Investigations of Orphan Drugs

Subpart C—Designation of an Orphan Drug

Subpart D—Orphan-drug Exclusive Approval

Subpart E—Open Protocols for Investigations

Subpart F—Availability of Information

Authority: Sections. 525, 526, 527, 528, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360aa, 360bb, 360cc, 360dd, 371).

Subpart A—General Provisions

§ 316.1 Scope of this part.

(a) This part implements sections 525, 526, 527, and 528 of the act and provides procedures to encourage and facilitate the development of drugs for rare diseases or conditions, including biological products and antibiotics. This part sets forth the procedures and requirements for:

(1) Submissions to FDA of:

(i) Requests for recommendations for investigations of drugs for rare diseases or conditions;

(ii) Requests for designation of a drug for a rare disease or condition; and

(iii) Requests for gaining exclusive approval for a drug product for a rare disease or condition.

(2) Allowing a sponsor to provide an investigational drug product under a treatment protocol to patients who need the drug for treatment of a rare disease or condition.

(b) This part does not apply to food, medical devices, or drugs for veterinary use.

(c) References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

§ 316.2 Purpose.

The purpose of this part is to establish standards and procedures for determining eligibility for the benefits provided for in section 2 of the Orphan Drug Act, including written recommendations for investigations of orphan drugs, a 7-year period of exclusive marketing, and treatment use of investigational orphan drugs. This part is also intended to satisfy Congress' requirements that FDA promulgate procedures for the implementation of sections 525(a) and 526(a) of the act.

§ 316.3 Definitions.

(a) The definitions and interpretations contained in section 201 of the act apply to those terms when used in this part.

(b) The following definitions of terms apply to this part:

(1) *Act* means the Federal Food, Drug, and Cosmetic Act as amended by section 2 of the Orphan Drug Act (sections 525–528 (21 U.S.C. 360aa–360dd)).

(2) *Active moiety* means the molecule or ion in a drug, excluding those appended portions of the molecule or drug that cause the drug to be an ester, salt, or other noncovalent derivative (such as a complex, chelate, or clathrate), that is responsible for the physiological or pharmacological action of the drug.

(3) *Clinically superior* means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved orphan drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an approved orphan drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials). Generally, this would represent the same kind of evidence needed to support a comparative effectiveness claim for two different drugs; in most cases, direct comparative clinical trials would be necessary; or

(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects. In some cases, direct comparative clinical trials will be necessary; or

(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

(4) *Director* means the Director of FDA's Office of Orphan Products Development.

(5) *FDA* means the Food and Drug Administration.

(6) *Holder* means the sponsor in whose name an orphan drug is designated and approved.

(7) *IND* means an investigational new drug application under part 312 of this chapter.

(8) *Manufacturer* means any person or agency engaged in the manufacture of a drug that is subject to investigation and approval under the act or the Public Health Service Act (42 U.S.C. 201 *et seq.*).

(9) *Marketing application* means an application for approval of a new drug filed under section 505(b) of the act, a request for certification of an antibiotic under section 507 of the act, or an application for a biological product/establishment license submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

(10) *Orphan drug* means a drug intended for use in a rare disease or condition as defined in section 526 of the act.

(11) *Orphan-drug designation* means FDA's act of granting a request for designation under section 526 of the act.

(12) *Orphan-drug exclusive approval* or *exclusive approval* means that, effective on the date of FDA approval as stated in the approval letter of a marketing application for a sponsor of a designated orphan drug, no approval will be given to a subsequent sponsor of the same drug product for the same indication for 7 years, except as otherwise provided by law or in this part.

(13) *Same drug* means:

(i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(ii) If it is a drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (but not necessarily all of the same structural features) as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug. This criterion will be applied as follows to different kinds of macromolecules:

(A) Two protein drugs would be considered the same if the only differences in structure between them were due to post-translational events or infidelity of translation or transcription or were minor differences in amino acid sequence; other potentially important differences, such as different glycosylation patterns or different tertiary structures, would not cause the drugs to be considered different unless the differences where shown to be clinically superior.

(B) Two polysaccharide drugs would be considered the same if they had identical saccharide repeating units, even if the number of units were to vary and even if there were post-polymerization modifications, unless the subsequent drug could be shown to be clinically superior.

(C) Two polynucleotide drugs consisting of two or more distinct nucleotides would be considered the same if they had an identical sequence of purine and pyrimidine bases (or their derivatives) bound to an identical sugar backbone (ribose, oxyribose, or modifications of these sugars), unless the subsequent drug were shown to be clinically superior.

(D) Closely related, complex partly definable drugs with similar therapeutic intent, such as two live viral vaccines for the same indication, would be considered the same unless the subsequent drug was shown to be clinically superior.

(14) *Sponsor* means the entity that assumes responsibility for a clinical or nonclinical investigation of a drug, including the responsibility for compliance with applicable provisions of the act and regulations. A sponsor may be an individual, partnership, corporation, or Government agency and may be a manufacturer, scientific institution, or an investigator regularly and lawfully engaged in the investigation of drugs. For purposes of the Orphan Drug Act, FDA considers the real party or parties in interest to be a sponsor.

Subpart B—Written Recommendations for Investigations of Orphan Drugs

§ 316.10 Content and format of a request for written recommendations.

(a) A sponsor's request for written recommendations from FDA concerning the nonclinical and clinical investigations necessary for approval ot a marketing application shall be submitted in the form and contain the

information required in this section. FDA may require the sponsor to submit information in addition to that specified in paragraph (b) of this section if FDA determines that the sponsor's initial request does not contain adequate information on which to base recommendations.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for written recommendations that contains the following:

(1) The sponsor's name and address.

(2) A statement that the sponsor is requesting written recommendations on orphan-drug development under section 525 of the act.

(3) The name of the sponsor's primary contact person and/or resident agent, and the person's title, address, and telephone number.

(4) The generic name and trade name, if any, of the drug and a list of the drug product's components or description of the drug product's formulation.

(5) The proposed dosage form and route of administration.

(6) A description of the disease or condition for which the drug is proposed to be investigated and the proposed indication or indications for use for such disease or condition.

(7) Current regulatory and marketing status and history of the drug product, including:

(i) Whether the product is the subject of an IND or a marketing application (if the product is the subject of an IND or a marketing application, the IND or marketing application numbers should be stated and the investigational or approved indication or indications for use specified);

(ii) Known marketing experience or investigational status outside the United States;

(iii) So far as is known or can be determined, all indications previously or currently under investigation anywhere;

(iv) All adverse regulatory actions taken by the United States or foreign authorities.

(8) The basis for concluding that the drug is for a disease or condition that is rare in the United States, including the following:

(i) The size and other known demographic characteristics of the patient population affected and the source of this information.

(ii) For drugs intended for diseases or conditions affecting 200,000 or more people in the United States, or for a vaccine, diagnostic drug, or preventive drug that would be given to 200,000 or more persons per year, a summary of the sponsor's basis for believing that the disease or condition described in paragraph (b)(6) of this section occurs so infrequently that there is no reasonable expectation that the costs of drug development and marketing will be recovered in future sales of the drug in the United States. The estimated costs and sales data should be submitted as provided in § 316.21(c).

(9) A summary and analysis of available data on the pharmacologic effects of the drug.

(10) A summary and analysis of available nonclinical and clinical data pertinent to the drug and the disease to be studied including copies of pertinent published reports.

(11) An explanation of how the data summarized and analyzed under paragraphs (b)(9) and (b)(10) of this section support the rationale for use of the drug in the rare disease or condition.

(12) A definition of the population from which subjects will be identified for clinical trials, if known.

(13) A detailed outline of any protocols under which the drug has been or is being studied for the rare disease or condition and a summary and analysis of any available data from such studies.

(14) The sponsor's proposal as to the scope of nonclinical and clinical investigations needed to establish the safety and effectiveness of the drug.

(15) Detailed protocols for each proposed United States or foreign clinical investigation, if available.

(16) Specific questions to be addressed by FDA in its recommendations for nonclinical laboratory studies and clinical investigations.

§ 316.12 Providing written recommendations.

(a) FDA will provide the sponsor with written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application if none of the reasons described in § 316.14 for refusing to do so applies.

(b) When a sponsor seeks written recommendations at a stage of drug development at which advice on any clinical investigations, or on particular investigations would be premature, FDA's response may be limited to written recommendations concerning only nonclinical laboratory studies, or only certain of the clinical studies (e.g., Phase 1 studies as described in § 312.21 of this chapter). Prior to providing written recommendations for the clinical investigations required to achieve marketing approval, FDA may require that the results of the nonclinical laboratory studies or completed early clinical studies be submitted to FDA for agency review.

§ 316.14 Refusal to provide written recommendations.

(a) FDA may refuse to provide written recommendations concerning the nonclinical laboratory studies and clinical investigations necessary for approval of a marketing application for any of the following reasons:

(1) The information required to be submitted by § 316.10(b) has not been submitted, or the information submitted is incomplete.

(2) There is insufficient information about:

(i) The drug to identify the active moiety and its physical and chemical properties, if these characteristics can be determined; or

(ii) The disease or condition to determine that the disease or condition is rare in the United States; or

(iii) The reasons for believing that the drug may be useful for treating the rare disease or condition with that drug; or

(iv) The regulatory and marketing history of the drug to determine the scope and type of investigations that have already been conducted on the drug for the rare disease or condition; or

(v) The plan of study for establishing the safety and effectiveness of the drug for treatment of the rare disease or condition.

(3) The specific questions for which the sponsor seeks the advice of the agency are unclear or are not sufficiently specific.

(4) On the basis of the information submitted and on other information available to the agency, FDA determines that the disease or condition for which the drug is intended is not rare in the United States.

(5) On the basis of the information submitted and on other information available to the agency, FDA determines that there is an inadequate basis for permitting investigational use of the drug under part 312 of this chapter for the rare disease or condition.

(6) The request for information contains an untrue statement of material fact.

(b) A refusal to provide written recommendations will be in writing and will include a statement of the reason for FDA's refusal. Where practicable, FDA will describe the information or material it requires or the conditions the sponsor must meet for FDA to provide recommendations.

(c) Within 90 days after the date of a letter from FDA requesting additional information or material or setting forth the conditions that the sponsor is asked to meet, the sponsor shall either:

(1) Provide the information or material or amend the request for written

recommendations to meet the conditions sought by FDA; or

(2) Withdraw the request for written recommendations. FDA will consider a sponsor's failure to respond within 90 days to an FDA letter requesting information or material or setting forth conditions to be met to be a withdrawal of the request for written recommendations.

Subpart C—Designation of an Orphan Drug

§ 316.20 Content and format of a request for orphan-drug designation.

(a) A sponsor that submits a request for orphan-drug designation of a drug for a specified rare disease or condition shall submit each request in the form and containing the information required in paragraph (b) of this section. A sponsor may request orphan-drug designation of a previously unapproved drug, or of a new orphan indication for an already marketed drug. In addition, a sponsor of a drug that is otherwise the same drug as an already approved orphan-drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug. More than one sponsor may receive orphan-drug designation of the same drug for the same rare disease or condition, but each sponsor seeking orphan-drug designation must file a complete request for designation as provided in paragraph (b) of this section.

(b) A sponsor shall submit two copies of a completed, dated, and signed request for designation that contains the following:

(1) A statement that the sponsor requests orphan-drug designation for a rare disease or condition, which shall be identified with specificity.

(2) The name and address of the sponsor; the name of the sponsor's primary contact person and/or resident agent including title, address, and telephone number; the generic and trade name, if any, of the drug or drug product; and the name and address of the source of the drug if it is not manufactured by the sponsor.

(3) A description of the rare disease or condition for which the drug is being or will be investigated, the proposed indication or indications for use of the drug, and the reasons why such therapy is needed.

(4) A discussion of the scientific rationale for the use of the drug for the rare disease or condition, including all data from nonclinical laboratory studies, clinical investigations, and other relevant data that are available to the sponsor, whether positive, negative, or inconclusive. Copies of pertinent unpublished and published papers are also required.

(5) Where the sponsor of a drug that is otherwise the same drug as an already-approved orphan drug seeks orphan-drug designation for the subsequent drug for the same rare disease or condition, an explanation of why the proposed variation may be clinically superior to the first drug.

(6) Where a drug is under development for only a subset of persons with a particular disease or condition, a demonstration that the subset is medically plausible.

(7) A summary of the regulatory status and marketing history of the drug in the United States and in foreign countries, e.g., IND and marketing application status and dispositions, what uses are under investigation and in what countries; for what indication is the drug approved in foreign countries; what adverse regulatory actions have been taken against the drug in any country.

(8) Documentation, with appended authoritative references, to demonstrate that:

(i) The disease or condition for which the drug is intended affects fewer than 200,000 people in the United States or, if the drug is a vaccine, diagnostic drug, or preventive drug, the persons to whom the drug will be administered in the United States are fewer than 200,000 per year as specified in § 316.21(b), or

(ii) For a drug intended for diseases or conditions affecting 200,000 or more people, or for a vaccine, diagnostic drug, or preventive drug to be administered to 200,000 or more persons per year in the United States, there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the United States as specified in § 316.21(c).

(9) A statement as to whether the sponsor submitting the request is the real party in interest of the development and the intended or actual production and sales of the product.

(c) Any of the information previously provided by the sponsor to FDA under subpart B of this part may be referenced by specific page or location if it duplicates information required elsewhere in this section.

§ 316.21 Verification of orphan-drug status.

(a) So that FDA can determine whether a drug qualifies for orphan-drug designation under section 526(a) of the act, the sponsor shall include in its request to FDA for orphan-drug designation under § 316.20 either:

(1) Documentation as described in paragraph (b) of this section that the number of people affected by the disease or condition for which the drug product is indicated is fewer than 200,000 persons; or

(2) Documentation as described in paragraph (c) of this section that demonstrates that there is no reasonable expectation that the sales of the drug will be sufficient to offset the costs of developing the drug for the U.S. market and the costs of making the drug available in the United States.

(b) For the purpose of documenting that the number of people affected by the disease or condition for which the drug product is indicated is fewer than 200,000 persons, "prevalence" is defined as the number of persons in the United States who have the disease or condition at the time of the submission of the request for orphan-drug designation. To document the number of persons in the United States who have the disease or condition for which the drug is to be indicated, the sponsor shall submit to FDA evidence showing:

(1) The estimated prevalence of the disease or condition for which the drug is being developed, together with an explanation of the sources of the estimate;

(2) The estimated prevalence of any other disease or condition for which the drug has already been approved or for which the drug is currently being developed, together with an explanation of the bases of these estimates; and

(3) The estimated number of people to whom the drug will be administered annually if the drug is a vaccine or for diagnosis or prevention of a rare disease or condition, together with an explanation of the bases of these estimates.

(c) When submitting documentation that there is no reasonable expectation that costs of research and development of the drug for the disease or condition can be recovered by sales of the drug in the United States, the sponsor shall submit to FDA:

(1) Data on all costs that the sponsor has incurred in the course of developing the drug for the U.S. market. These costs shall include, but are not limited to, nonclinical laboratory studies, clinical studies, dosage form development, record and report maintenance, meetings with FDA, determination of patentability, preparation of designation request, IND/marketing application preparation, distribution of the drug under a "treatment" protocol, licensing costs, liability insurance, and overhead

and depreciation. Furthermore, the sponsor shall demonstrate the reasonableness of the cost data. For example, if the sponsor has incurred costs for clinical investigations, the sponsor shall provide information on the number of investigations, the years in which they took place, and on the scope, duration, and number of patients that were involved in each investigation.

(2) If the drug was developed wholly or in part outside the United States, in addition to the documentation listed in paragraph (c)(1) of this section:

(i) Data on and justification for all costs that the sponsor has incurred outside of the United States in the course of developing the drug for the U.S. market. The justification, in addition to demonstrating the reasonableness of the cost data, must also explain the method that was used to determine which portion of the foreign development costs should be applied to the U.S. market, and what percent these costs are of total worldwide development costs. Any data submitted to foreign government authorities to support drug pricing determinations must be included with this information.

(ii) Data that show which foreign development costs were recovered through cost recovery procedures that are allowed during drug development in some foreign countries. For example, if the sponsor charged patients for the drug clinical investigations, the revenues collected by the sponsor must be reported to FDA.

(3) In cases where the drug has already been approved for marketing for any indication or in cases where the drug is currently under investigation for one or more other indications (in addition to the indication for which orphan-drug designation is being sought), a clear explanation of and justification for the method that is used to apportion the development costs among the various indications.

(4) A statement of and justification for any development costs that the sponsor expects to incur after the submission of the designation request. In cases where the extent of these future development costs are not clear, the sponsor should request FDA's advice and assistance in estimating the scope of nonclinical laboratory studies and clinical investigations and other data that are needed to support marketing approval. Based on these recommendations, a cost estimate should be prepared.

(5) A statement of and justification for production and marketing costs that the sponsor has incurred in the past and expects to incur during the first 7 years that the drug is marketed.

(6) An estimate of and justification for the expected revenues from sales of the drug in the United States during its first 7 years of marketing. The justification should assume that the total market for the drug is equal to the prevalence of the disease or condition that the drug will be used to treat. The justification should include:

(i) An estimate of the expected market share of the drug in each of the first 7 years that it is marketed, together with an explanation of the basis for that estimate;

(ii) A projection of and justification for the price at which the drug will be sold; and

(iii) Comparisons with sales of similarly situated drugs, where available.

(7) The name of each country where the drug has already been approved for marketing for any indication, the dates of approval, the indication for which the drug is approved, and the annual sales and number of prescriptions in each country since the first approval date.

(8) Verification by an independent certified public accountant of the data, estimates, and justifications submitted pursuant to this section. The certified public accountant must verify that the data are accurate and valid, that the estimates and justifications are reasonable, and that both the data and estimates follow generally accepted accounting practices and procedures.

(d) A sponsor that is requesting orphan-drug designation for a drug designed to treat a disease or condition that affects 200,000 or more persons shall, at FDA's request, allow FDA or FDA-designated personnel to examine at reasonable times and in a reasonable manner all relevant financial records and sales data of the sponsor and manufacturer.

§ 316.22 Permanent-resident agent for foreign sponsor.

Every foreign sponsor that seeks orphan-drug designation shall name a permanent resident of the United States as the sponsor's agent upon whom service of all processes, notices, orders, decisions, requirements, and other communications may be made on behalf of the sponsor. The permanent-resident agent may be an individual, firm, or domestic corporation and may represent any number of sponsors. The name of the permanent-resident agent shall be provided to: Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 316.23 Timing of requests for orphan-drug designation; designation of already approved drugs.

(a) A sponsor may request orphan-drug designation at any time in the drug development process prior to the submission of a marketing application for the drug product for the orphan indication.

(b) A sponsor may request orphan-drug designation of an already approved drug product for an unapproved use without regard to whether the prior marketing approval was for an orphan-drug indication.

§ 316.24 Granting orphan-drug designation.

(a) FDA will grant the request for orphan-drug designation if none of the reasons described in § 316.26 for requiring or permitting refusal to grant such a request applies.

(b) When a request for orphan-drug designation is granted, FDA will notify the sponsor in writing and will publicize the orphan-drug designation in accordance with § 316.28.

§ 316.25 Refusal to grant orphan-drug designation.

(a) FDA will refuse to grant a request for orphan-drug designation if any of the following reasons applies:

(1) The drug is not intended for a rare disease or condition because:

(i) There is insufficient evidence to support the estimate that the drug is intended for treatment of a disease or condition in fewer than 200,000 people in the United States, or that the drug is intended for use in prevention or in diagnosis in fewer than 200,000 people annually in the United States; or

(ii) Where the drug is intended for prevention, diagnosis, or treatment of a disease or condition affecting 200,000 or more people in the United States, the sponsor has failed to demonstrate that there is no reasonable expectation that development and production costs will be recovered from sales of the drug for the orphan indication in the United States. A sponsor's failure to comply with § 316.21 shall constitute a failure to make the demonstration required in this paragraph.

(2) There is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition.

(3) A drug that is otherwise the same drug as one that already has orphan-drug exclusive approval for the same rare disease or condition and the

sponsor has not submitted a medically plausible hypothesis for the possible clinical superiority of the subsequent drug.

(b) FDA may refuse to grant a request for orphan-drug designation if the request for designation contains an untrue statement of material fact or omits material information.

§ 316.26 Amendment to orphan-drug designation.

At any time prior to approval of a marketing application for a designated orphan drug, the sponsor may apply for an amendment to the indication stated in the orphan-drug designation for the drug. FDA will allow any such amendment if FDA finds that the initial designation request was made in good faith, if it finds that the amendment is intended solely to conform the orphan drug indication to the results of unanticipated test data, and if it finds that the amendment does not render the drug ineligible for orphan-drug designation because the prevalence of the condition or disease named in the amendment exceeds 200,000 people in the United States as of the date of submission of the amendment request.

§ 316.27 Change in ownership of orphan-drug designation.

(a) A sponsor may transfer ownership of or any beneficial interest in the orphan-drug designation of a drug to a new sponsor. At the time of the transfer, the new and former owners are required to submit the following information to FDA:

(1) The former owner or assignor of rights shall submit a letter or other document that states that all or some rights to the orphan-drug designation of the drug have been transferred to the new owner or assignee and that a complete copy of the request for orphan-drug designation, including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation, has been provided to the new owner or assignee.

(2) The new owner or assignee of rights shall submit a statement accepting orphan-drug designation and a letter or other document containing the following:

(i) The date that the change in ownership or assignment of rights is effective;

(ii) A statement that the new owner has a complete copy of the request for orphan-drug designation including any amendments to the request, supplements to the granted request, and correspondence relevant to the orphan-drug designation; and

(iii) A list of the rights that have been assigned and those that have been reserved. This may be satisfied by the submission of copies of all relevant agreements.

(iv) The name and address of a new primary contact person or resident agent.

(b) No sponsor may relieve itself of responsibilities under the Orphan Drug Act or under this part by assigning rights to another person without:

(1) Assuring that the sponsor or the assignee will carry out such responsibilities; or

(2) Obtaining prior permission from FDA.

§ 316.28 Publication of orphan-drug designations.

FDA will publish the following information about designated orphan drugs through an annually updated list in the **Federal Register:**

(a) The name and address of the manufacturer and sponsor;

(b) The generic name and trade name, if any, of the drug and the date of the granting of orphan-drug designation;

(c) The rare disease or condition for which orphan-drug designation was granted; and

(d) The proposed indication for use of the drug.

§ 316.29 Suspension or revocation of orphan-drug designation.

(a) FDA may suspend or revoke orphan-drug designation for any drug if the agency finds that:

(1) The request for designation contained an untrue statement of material fact; or

(2) The request for designation omitted material information required by this part; or

(3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor.

(b) For an approved drug, suspension or revocation of orphan-drug designation also suspends or withdraws the sponsor's exclusive marketing rights for that drug but not the approval of the drug's marketing application.

(c) Where a drug has been designated as an orphan drug because the prevalence of a disease or condition (or, in the case of vaccines, diagnostic drugs, or preventive drugs, the target population) is under 200,000 in the United States at the time of designation, its designation will not be revoked on the ground that the prevalence of the disease or condition (or the target population) becomes more than 200,000 persons.

Subpart D—Orphan-drug Exclusive Approval

§ 316.30 Scope of orphan-drug exclusive approval.

(a) After approval of a sponsor's marketing application for a designated orphan-drug product for treatment of the rare disease or condition concerning which orphan-drug designation was granted, FDA will not approve another sponsor's marketing application for the same drug before the expiration of 7 years from the date of such approval as stated in the approval letter from FDA, except that such a marketing application can be approved sooner if, and such time as, any of the following occurs:

(1) Withdrawal of exclusive approval or revocation of orphan-drug designation by FDA under any provision of this part; or

(2) Withdrawal for any reason of the marketing application for the drug in question; or

(3) Consent by the holder of exclusive approval to permit another marketing application to gain approval; or

(4) Failure of the holder of exclusive approval to assure an adequate supply of the drug under section 527 of the act and § 316.36.

(b) If a sponsor's marketing application for a drug product is determined not to be approvable because approval is barred under section 527 of the act until the expiration of the period of exclusive marketing of another drug product, FDA will so notify the sponsor in writing.

§ 316.34 FDA recognition of exclusive approval.

(a) FDA will send the sponsor (or, the permanent-resident agent, if applicable) timely written notice recognizing exclusive approval once the marketing application for a designated orphan drug product has been approved. The written notice will inform the sponsor of the requirements for maintaining orphan-drug exclusive approval for the full 7-year term of exclusive approval.

(b) When a marketing application is approved for a designated orphan-drug that qualifies for exclusive approval, FDA will publish in its publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" information identifying the sponsor, the drug, and the date of termination of the orphan-drug exclusive approval. A subscription to this publication and its monthly cumulative supplements is available from the Superintendent of Documents, Government Printing Office, Washington, DC 20402–9325.

§ 316.36 Inadequate supplies of orphan drugs.

(a) Under section 527 of the act, whenever the Director has reason to believe that the holder of exclusive approval cannot assure the availability of sufficient quantities of an orphan drug to meet the needs of patients with the disease or condition for which the drug was designated, the Director will so notify the holder of this possible insufficiency and will offer the holder one of the following options, which must be exercised by a time that the Director specifies:

(1) Provide the Directory in writing, or orally, or both, at the Director's discretion, views and data as to how the holder can assure the availability of sufficient quantities of the orphan drug within a reasonable time to meet the needs of patients with the disease or condition for which the drug was designated; or

(2) Provide the Director in writing the holder's consent for the approval of other marketing applications for the same drug before the expiration of the 7-year period of exclusive approval.

(b) If, within the time that the Director specifies, the holder fails to consent to the approval of other marketing applications and if the Director finds that the holder has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated, the Director will issue a written order withdrawing the drug product's exclusive approval. This order will embody the Director's findings and conclusions and will constitute final agency action. An order withdrawing the sponsor's exclusive marketing rights may issue irrespective of whether there are other sponsors that can assure the availability of alternative sources of supply. Once withdrawn pursuant to this section, exclusive approval may not be reinstated for that drug.

Subpart E—Open Protocols for Investigations

§ 316.40 Treatment use of a designated orphan drug.

Sponsors that have received orphan-drug designation may obtain treatment use for designated drugs as provided in § 312.34 of this chapter.

Subpart F—Availability of Information

§ 316.50 Guidelines.

FDA's Office of Orphan Products Development will maintain and make publicly available a list of guidelines that apply to the regulations in this part. The list states how a person can obtain a copy of each guideline. A request for a copy of the list or for any guideline should be directed to the Office of Orphan Products Development (HF-35), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

§ 316.52 Availability for public disclosure of data and information in requests and applications.

(a) FDA will not publicly disclose the existence of a requesat for orphan-drug designation under section 526 of the act prior to final FDA action on the request unless the existence of the request has been previously publicly disclosed or adknowledged.

(b) Irrespective of whether the existence of a pending request for designation has been publicly disclosed or acknowledged, no data or information in the request are available for public disclosure prior to final FDA action on the request.

(c) Upon final FDA action on a request for designation, FDA will determine the public availability of data and information in the request in accordance with part 20 and § 314.430 of this chapter and other applicable statutes and regulations.

(d) In accordance with § 316.28, FDA will publish in the **Federal Register** a list of all orphan-drug designations. This list will be updated annually.

(e) FDA will not publicly disclose the existence of a pending marketing application for a designated orphan drug for the use for which the drug was designated unless the existence of the application has been previously publicly disclosed or acknowledged.

(f) FDA will determine the public availability of data and information contained in pending and approved marketing applications for a designated orphan drug for the use for which the drug was designated in accordance with part 20 and § 314.430 of this chapter.

Dated: January 14, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

Louis W. Sullivan,

Secretary of Health and Human Services.

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